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on Biotechnology Safety

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SAFETY GUIDELINES AND PROCEDURES FOR BIOSCIENCE-BASED INDUSTRY AND OTHER APPLIED MICROBIOLOGY*

Prepared by

the UNIDO secretariat

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SUMMARY

General Objective

The purpose of the UNIDO/WHO/UNEP working group on safety measures for biotechnology research and industry is to establish a process through which the potential risks arising from this rapidly evolving technology can be assessed and appropriate safety measures designed. While doing so it is emphasized that biotechnology, with its advanced techniques of genetic engineering, holds great promise for all nations of the world, particularly the developing countries. For this reason, safety measures should be consistent with the degree of anticipated risk and not be made as to hinder needed developments.

Specific Objectives

1. Consider whether genetically engineered organisms pose added risks to researchers, workers and public.

2. Consider whether immuno-suppressed persons are at added risk if performing biotechnology R+D or working for bioscience-based industry.

3. Consider whether new, unique substances produced via biotechnology will pose added risks to workers or public.

4. Consider whether there are risks associated with the growing of cell lines and hybridomas for the production of monoclonal antibodies.

5. Consider whether bio-wastes disposal pose any particular risks.

6. Consider whether to consider the issue of deliberately releasing genetically engineered microorganisms into the environment.

7. In view of the foregoing, consider existing risk assessment schemes and determine their suitability to assessing risks associated with biotechnology R+D and with bioscience-based industry.

8. Consider existing rules and regulations pertaining to pertinent industries in order to evaluate whether these are adequate to manage bioscience-based industry.

9. Suggest improvements as necessary if the existing body of rules and regulations is deemed insufficient or inadequate.

10. In case entirely new guidelines and/or procedures need to be desinged in order to manage bioscience-based industry, formulate general recommendations as to their contents.

11. Consider whether biotechnology R+D and applications pose any special problems to or in developing countries that should be dealt with apart from concerns related to developed countries.

12. Consider how the recommendations being made by the UNIDO/WHO/UNEP working group will be legitimized and given wide-ranging support.

13. Consider the future role of the ICGEB in formulating safety procedures, guidelines and to monitor national rules and regulations.

I. Introduction

UNIDO has since its inception been involved in several aspects of applied microbiology. However, after 1981 this type of activity has been significantly expanded as the organization initiated a series of measures, the objective of which was, and remains, to make certain the fruits likely to emanate from advanced biotechnology R+D, including genetic engineering, would be shared by developing countries. The most important initiative being undertaken is to establish and make operational the International Centre for Genetic Engineering and Biotechnology (ICGEB) in two components located in New Delhi, India and Trieste, Italy. As of this writing, 36 countries belong to the ICGEB and several more will undoubtedly join in the near future. Further, operational activities will begin in provisional ICGEB facilities as early as the beginning of 1986.

During the preparatory work for the ICGEB, the matter of safe laboratory practices, especially as they pertain to research on genetically engineered microorganisms, became a matter of concern to UNIDO. As several countries offered to host the ICGEB and/or its affiliated centres, it became clear that national legislation which were aimed at ensuring safe laboratory practices varied from almost no control to control measures akin to U.S. or U.K. guidelines. As the time grows ever shorter before research begins at both ICGEB and at its affiliates, the matter of drawing up and applying adequate and uniform safety rules and practices throughout the ICGEB system takes on an air of urgency. Futher, since research at the ICGEB and its affiliates is to be of an applied nature, and since products and processes will ensue as soon as practicable, there is also a need to consider safety rules and practices as they may be applicable to bioscience-based industry (and to industry which will utilize the advanced biotechnology techniques).

While UNIDO has by definition an interest in safety practices as they relate to industry, it is also aware of the concerns the World Health Organization (WHO) has in this area as they relate to health and safety. Particular note has been made of the publication Laboratory Biosafety Manual (1) with its guidelines pertaining to laboratory practices, transfer and shipping of specimens, guide to biosafety equipment, etc., and the report by WHO's Regional Office for Europe

"Health Impact of Biotechnology" (2). Overlapping interests between the two organizations led to the establishment of continous communications between UNIDO and WHO's programme Safety Measures in Microbiology. Eventually, it was decided between the two to constitute a working group and begin a systematic study on whether a set of rules and practices could and should be elaborated, the applications of which could be recommended to all countries.

More recently, UNIDO became acquainted with the interest that the United Nations Environment Programme (UNEP) has in the topics of bio-wastes disposal and the deliberate release of genetically engineered organisms into the environment. In view of the obvious overlap of interests, UNEP was informed of the planned UNIDO/WHO working group and asked if it would be interested to partake in its activities. The response was positive and, after consultations with WHO, it was decided between the three to quickly constitute a UNIDO/WHO/UNEP working group to consider all facets of microbiological safety pertaining to research institutions and industry.

In view of the foregoing, the UNIDO staff in this document presents its ideas on the subject, stressing those which apply to industry and industrialization. Accordingly, this paper begins with a section on risk and risk assessment, continues with some thoughts on risks that could be associated with applied microbiology, then concludes with a few suggestions for activities to be undertaken by the UNIDO/WHO/UNEP working group.

II. Risk and Risk Assessment

Risk, as it is here understood, is a measure of the probability of sustaining injury or death in the course of, or because of, research activity or activities pertaining to bioscience-based industry. Risk assessment is the attempt to determine as exactly as possible how high or low this probability is of being realized. Risk assessment schemes can be based on data used by the chemical and pharmaceutical industries to develop such concepts as "no observed effect levels", "acceptable daily intake", "permissible exposure limits", and LD_{50} (lethal level for 50 per cent of the exposed population).

Of direct pertinence to microbiological research and industrial activity is the classification system developed by WHO to classify microorganisms in one of four risk groups, with Risk Group I consisting of microorganisms believed unlikely to cause human disease or animal disease of veterinary importance, while Risk Group IV includes pathogens "...that usually produces serious human animal diseases and may be readily transmitted from one individual to another, directly or indirectly" (3). Once the microorganism(s) for use either in a research project or for industrial purposes has been classified, it should be possible to define the conditions under which work with that organism would proceed. However, shortcomings of this scheme as it relates to the concerns of the UNIDO/WHO/UNEP working group may include, (1) disease agents which affect plants are not included, and (2) a genetically engineered microorganism may not easily fit into a risk group, at least until after it has been studied closely.

Guidelines now being drafted by the World Bank for identifying, analyzing and controlling dangerous industrial installations (3) will also be of interest to the working group. It is expected that a two level system will be developed: the first consists of industrial plants that employ hazardous substances above a certain threshold level and that will therefore be obliged to notify the World Bank, while the second level consist of "full safety cases" - i.e. plants that use hazardous substances in such quantities or which are so dangerous that full safety use assessments have to be performed. According to one account, the objectives of the "full safety cases" are: "to identify the nature and scale of the use of dangerous substances at the installation; to give an account of the arrangements for safe operation and for control of serious deviations that could lead to an accident; to identify the type, relative likelihood and broad consequences of mishaps that might occur; and to demonstrate that the developer has appreciated the major hazard potential of the company's activities and has considered whether the controls are adequate" (4).

Though the World Bank guidelines are being drawn up primarily for chemical industrial plants, they would appear to also be at least partially useful for bioscience-based industry, taking into consideration that microorganisms used in and by industry present different problems than do chemicals.

Aside from the WHO classification system and the as yet unseen World Bank guidelines, traditional risk assessment schemes may not be so useful when regarding the bioscience-based industry since they may present the following shortcomings:

- Historial statistical data indicative of causal relationships between exposure to a substance and injury does not exist in bioscience-based industry when considering genetic engineering techniques.

- Accidents which expose workers to a substance (or radiation) have many times served the useful purpose of providing reliable data pertaining to conditions of exposure and their effects. Available information indicates that accidents in the bioscience-based industry have so far proven benign. However, it is difficult to incorporate negative data in risk assessments.

- The conditions of exposure (level, frequency, duration and route) that are tested in animal models are different from the conditions of actual human exposure (themselves poorly defined even in established industry). The situation in regard to genetically engineered organisms and the substances they produce is that virtually no data is available from either animal models or from experimentally induced injuries.

- No data is available to the bioscience-based industry from epidemiological investigations of chronic exposure or injury, and very little such data can be expected in the next 5-10 years.

In view of these shortcomings (and from others that cannot here be described) it may be that the UNIDO/WHO/UNEP working group will have to formulate new procedures for risk assessment in reference to biotechnology, including genetic engineering, and the industries which will employ it.

III. Conjectural Risks Associated with Applied Biotechnology

Following is a preliminary listing of research and industrial activities involving biotechnology, including genetic engineering, that may pose risks. Throughout it must be kept in mind that laboratory personnel and workers are the ones who are the most at risk.

1. Risks associated with the construction and propagation of new organisms.

The conjectural hazards of constructing and manipulating new microorganism were extensively debated during the recombinant DNA (rDNA) controversy and as a result a sizeable body of evidence was built up demonstrating the low or non-existent risk of rDNA research. Nevertheless, as a result of voiced public concerns and because it was thought prudent safety procedures to manage perceived risky research were developed and implemented to guarantee the safety of laboratory personnel and public. While recognizing that an essential difference exists between research and industrial practices (in research the objective is to examine whether or not transformation takes place while in industrial processes the genetically engineered organisms resulting from research are used), this existing body of evidence may be used by the UNIDO/WHO/UNEP group to lay an objective foundation for the consideration of the large-scale production of genetically engineered organisms. However, it is doubtful whether information from this source may be applicable to the consideration of genetically manipulated plants and animals. Since plants are already being genetically engineered, it will be necessary to rather quickly come to grips with regulatory issues pertaining to the growing of genetically engineered plants, both in greenhouses and in fields.

2. Risks associated with the use of unique strains for industrial production.

It is axiomatic among infectious disease specialists that the larger the number of disease-causing organisms an individual is exposed to, the greater the likelihood of him contracting the disease. One may

wonder if an analogous situation could arise as bicscience-based firms use extremely large numbers of unique organisms in industrial processes and bioscience workers, in case of mishaps, become exposed to them. Further, the question of immuno-surpressed persons has not been adequately addressed. These persons (an ever-increasing number including, for example, diabetics and those being treated with antibiotics or anti-cancer drugs) often are attacked by organisms innocuous to normal persons. Will these persons face increased risks when exposed to genetically engineered organisms?

Industrial practices differ from research in that they do not take place in standardized cabinets or in small volumes. It is probable that industrial equipment much like that used in the present fermentation industry will be used to process genetically engineered organisms. If so, it will probably be prudent to examine whether this equipment is adequate from a safety viewpoint when genetically engineered organisms are processed in very large volumes.

3. Risks associated with the products obtained from the new strains.

The question may be asked whether products now being made available through biotechnological means of manufacture, that have not previously existed, will pose new hazards to workers and the public. It is doubtful whether specific measures for the physical containment of genetically engineered organisms will have to vary from those now used in, for example, the pharmaceutical industry. Similarly, existing regulations governing the safety testing and labelling of new drugs and food additives will probably be sufficient to regulate similar substances produced through new biotechnology. Yet, the question remains if there is likely to be any additional risks associated with new products. Perhaps additional hazards could appear as a result of unique substances, produced for the first time, proving to be powerful allergens or auto-immunogens, with bioscience workers the most likely to be intially threatened.

4. Risks associated with the propagation of hybridomas.

At the time of this writing, apparently no one has sounded any warnings about risks associated with growing hybridomas in industrial quantities. Nevertheless, it may be worthwhile for the UNIDO/WHO/UNEP working group to investigate this area in order to assess if in the future, risky processes or products may be developed.

5. Risks associated with the disposal of bio-wastes.

Some bioscience industrial practices will produce no dangerous wastes, for example, those during which the cells are ruptured to recover the desired protein. Other practices may pose problems with disposal of wastes, in particular those using bacteria and yeast that secrete the desired substances into the substrate and are thus still viable at the end of their useful life. The UNIDO/WHO/UNEP group may wish to consider the formulation of safety criteria for bio-wastes disposal including setting standards for permissible concentrations of chemicals, proof of non-viableness of organisms to be disposed of and other variables.

6. Risks associated with the deliberate release of genetically engineered microorganisms into the environment.

The question of the large-scale release of genetically engineered organisms into the environment may also have to be dealt with. Already persmission has been sought to spray a huge number of genetically engineered organisms on plants to prevent frost damage. In the near future similar requests will be made to perform field trials in order to enhance oil recovery, to recover metals and minerals from different low-quality sources, and to fight insects and weeds. Will unique genetically engineered organisms stay in the niches they are designed for, or is there a possibility one (or more) of them could spread, causing unanticipated damage? In view of the contentious nature of this issue, care will have to be taken how the working group will attempt to deal with it.

In concluding this section, a special mention will be made of one of the conclusions made in the aforementioned WHO report, namely that the "...conjectural risks of the application of recombinant DNA and other techniques to biotechnology can be assessed and managed with current risk assessment strategies and control methods"(5). If this is the case, these available methods would still have to be altered or adjusted to take into account the unique characteristics given to biotechnology due to the discovery and application of genetic engineering techniques. In particular, the lack of data on long-term effects (as pointed out above) makes for an incomplete risk assessment. Therefore, it may be adviceable to try to formulate a "new" risk assessment scheme that could be considered "organic" in that it will become incrementally improved with time as new data becomes available and is taken into account. At first it may be that the scheme will be based largely on empirical observations and the subjective opinions by researchers, technologists, and other industrial practitioners. However, with the passage of time and as data accumulates from both directed research and industrial operations, the scheme will become more and more based on objective criteria.

Once a risk assessment scheme has been formulated and put into practice, it should be possible to characterize the nature and magnitude of the risks associated with the practices of bioscience-based industry and to calculate the degree of confidence associated with the analysis. These will provide the basis for attempting risk management; i.e., concrete attempts by UNIDO/WHO/UNEP working group to formulate control measures applicable to the bioscience-based industry. Initially, the working group may consider two components of risk management. First, whether or not the assessed risk is important. The magnitude of importance will probably have to be determined not only on the calculated probability of the risk but also on the degree of confidence one can place on the data underlying the risk assessment. Second, if the decision is made that the assessed risk, or risks, is sufficiently important to worry about, then the working group will have to decide how and to what extent measures are required to sufficiently manage the risk(s).

IV. Safety Measures Related to Biotechnology R+D and to Bioscience-based Industry

The history of industrialization shows that when some industries have been poorly or not at all regulated, society and the environment have suffered. The experiences with the chemical (including pesticide) industry are particularly illuminative. In view of the historic necessity of regulating some industry, it is reasonable to investigate whether bioscience-based industry should be managed by society. If so, the main questions which face the UNIDO/WHO/UNEP working group are: (1) whether existing rules and guidelines are adequate in themselves to regulate biotechnology R+D and the new bioscience-based industry; (2) whether these rules and guidelines are deficient but may be used as a base upon which to formulate improved guidelines and procedures; or (3) whether a completely new set of guidelines and procedures will have to be formulated since the modern bioscience-based industry has unique characteristics and therefore poses unique problems. A subsidiary question, when considering these main questions, is whether research and industrial activities that is being, or is likely to be, undertaken in developing countries pose any special problems that require special answers.

1. Adequacy of existing rules and guidelines.

The working group may wish to regard existing national rules and guidelines and assess whether any or all of them are adequate to manage research and industry. Given the limited resources that will probably be available to the working group, it will be impossible to more than sample national laws in this area. It is likely that an OECD study presently underway (6) will adequately cover the applicable laws and rules in developed countries. As to developing countries, a suggestion may be made to use the information provided by countries which have nominated national institutions for affiliation with the ICGEB. A reasonable request can be made to these governments to provide information pertaining to the safety practices of R+D institutions and the laws and rules which govern their management in order to make certain the candidate institution will fulfil minimal criteria of safety. If the

working group's mandate is of a lengthy duration, it may consider to formulate a mechanism for monitoring national laws and rules as they evolve with the advance of biotechnology and its applications.

2. Improvements of existing rules and guidelines.

After a sample of national laws and rules has been appraised, it should be possible to identify shortcomings pertaining to biotechnology R+D and industry. Shortcomings may range from being inconsequential to serious gaps. But the important part will be to find out whether there are generic shortcomings and, if so, whether there are possibilities for recommending palliative corrective measures applicable to most of them.

3. Creating a new set of rules and procedures.

If existing management measures are found completely inappropriate or deficient, new measures may have to be formulated and applied. This task would obviously be beyond the possibility of the working group to take on. In this case, the group could consider making a recommendation for the creation of new measures by competent authorities and, additionally, could suggest general guidelines on how they should be constructed.

Whatever approach is taken for designing improved or new safety measures, account has to be taken of the dynamism of biotechnology. Since the field is evolving so rapidly and since all new developments cannot be predicted, it is important that measures be flexible and amenable to change. A useful lesson of flexibility may be the gradual relaxation of the NIH guidelines (and the other national measures based on them) that has taken place as new data became available demonstrating the safety of recombinant DNA.

V. Concluding Thoughts

It is probable that most rules which now exist pertaining to applied microbiology are those which have been formulated either to regulate existing industries, particularly those related to pharmaceuticals and chemicals, or to protect the environment. In

addition, as a result of the public concern over rDNA research in the late 1970s, many nations elaborated guidelines regulating such research (the UK and US in 1976 and Japan in 1979).

After approximately nine years of existing with and taking account of rDNA rules and regulations, their value (or lack of) is still being discussed. A sizeable group of scientists believe that rDNA research poses no hazards to society and that the rules which came into existence were hurriedly contrived to appease a vocal few who managed to sensationalize their views. These rules, in the thinking of these scientists, serve no good purpose but only tend to hinder legitimate research and researchers. Conversely, there are those who believe that the existing rules do not go far enough, that they were promulgated by scientists themselves who were only intent on protecting their interests and the public be damned.

The reason why this wide divergence of views on rDNA rules is here mentioned is that it alludes to the question whether there is an overriding necessity for promulgating additional safety guidelines and procedures for the bioscience-based industry. Since there are likely to be both those who will decry the need for such guidelines and those who may wish to see the adoption of very stringent rules and regulations, this question has to be considered in depth by the UNIDO/WHO/UNEP working group and if the decision is to go ahead, it will have to be based on sound reasoning.

A point that should be made is regarding the legitimization of the safety guidelines and procedures that may be formulated by the UNIDO/WHO/UNEP working group. Though biotechnology has been part of human endeavours for thousands of years the recent rDNA controversy and sensationalist stories in the popular press about eugenics have caused the public to equate biotechnology with rDNA, eugenics and, less precisely, "tinkering with genes" or "fooling around with mother nature". For these reasons, it may be worthwhile for the group to consider some type of a public information programme which would have as its aim the informing of scientists, decision-makers and the general public of the measures which it has taken and how they relate to guaranteeing the safety of bio-industrial practices. In order to give a

sense of authority to the measures taken, it is important that eminent scientists and non-scientists take part in the workings of the UNIDO/WHO/UNEP group and subsequently, are mobilized in a supporting campaign to have the resulting safety guidelines and procedures widely understood and accepted.

Lastly, the group may wish to consider whether the ICGEB could take on one or more functions in regards to either risk assessment or the elaboration of safety management measures, or both. Since its membership is global and since it is, by the definition of its Statutes, to be a research centre of high excellence, it could be the legitimizing authority to the work of the group. Eventually, it may be appropriate for the ICGEB to take over the mandate from the UNIDO/WHO/UNEP working group and perpetuate its work. Simultaneously, it could assume the tasks of continiously monitoring national laws and regulations related to biotechnology safety and to collect and collate information on long-term effects, if any appear in the laboratories or industries.

Footnotes and Bibliography

1. WHO, Laboratory Biosafety Manual, (Geneva: WHO, 1983).

2. "Health Impact of Biotechnology", Report on a WHO Working Group, Dublin, 19 November 1982, in Swiss Biotech, vol. 2, No. 5, 1984, pp. 7 - 32.

3. "New Code on Plant Hazards in Third World", European Chemical News, 18 March 1985, p. 19.

4. Ibid.

5. "Health Impact of Biotechnology", op.cit., p.8.

6. OECD has been performing a study on conjectural risks and regulations associated with biotechnology since 1984. The report is, as of this writing, expected to be released in the fall of 1985.

Additional Sources

"Safe Biotechnology - General Considerations", a Report prepared by the Safety in Biotechnology Working Party of the European Federation of Biotechnology, 1984.

Office of Technology Assessment, Commercial Biotechnology, An International Analysis, (Washington D.C.: OTA, 1984), pp. 355 - 380.

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BIOSAFETY GUIDELINES FOR MANUFACTURE OF VACCINES AND BIOLOGICALS *

Prepared by

the World Health Organization

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INTRODUCTION

The recent advances in molecular biology have prompted the World Health Organization to assess these regarding public health application. Primary considerations have been targetted to the field of infectious diseases. As a result new or expanded initiatives have been established within WHO's Division of Communicable Diseases. These include:

1. WHO Programme for Vaccine Development;
2. New rapid diagnostic techniques;
3. Transfer of vaccine production technology to developing countries.

With these initiatives there is the commitment of the Organization to assure the safety of the product, the safety of the biotechnology industry worker, and the safety of the community from possible hazardous discharges from the industry.

WHO is called on by its constitution "to develop, establish and promote international standards with respect to ... biological ... products." Accordingly, WHO sets international biological standards and provides relevant information to national health authorities so that national standards, calibrated in international units, can be established. Through this process WHO will assure that vaccines and other biological products developed through its programmes and others offered through international trade will be safe for use by the general public.

To meet the worker and community safety requirements, WHO's Seventh General Programme of Work calls for the provision of safety guidelines for biotechnology organizations producing vaccines and biological products. Accordingly draft biosafety guidelines are being considered for laboratories and industries engaged in the manufacture or preparation of vaccines and biologicals where:

1. the process uses organisms or cells which contain foreign DNA inserted by the recombinant DNA technique;
2. the volume of culture, medium or tissue is larger than 10 litres. This definition includes the use of continuous culture where the volume of the culture vessel or of the spent culture is greater than 10 litres, and

3. the work is carried out within contained facilities.

While the proposed guidelines are primarily directed towards fermentation technology, the containment specifications and other practices may be used as a basis to derive similar containment standards for other technologies. The guidelines apply only to minimum practices and physical containment.

Existing national guidelines for large scale production of vaccines and biological products are serving as the basis of the WHO effort. However, development of the WHO guidelines is currently in abeyance to ascertain if similar guidelines being developed by the OECD or under discussion with UNIDO and UNEP would serve WHO's needs.

PROGRAMME FOR VACCINE DEVELOPMENT
RESEARCH PRIORITIES

The WHO Programme for Vaccine Development is a goal-oriented-programme which funds research only in the following priority areas:

1. Acute viral respiratory diseases of childhood

(a) Molecular cloning of individual genes of parainfluenza virus type 3 and respiratory syncytial virus.

(b) Nucleotide sequencing of the genes specifying the immunologically important polypeptides (presumed to be the two surface glycoproteins and the nucleoprotein) and subsequently the other genes and inter-cistronic regions.

(c) Expression of cloned viral genes in prokaryotic systems (to produce high yields of unprocessed polypeptides) and eukaryotic systems (for modified proteins).

(d) Production and characterization of monoclonal antibodies for definition of epitopes and for use in affinity chromatography for purification of viral polypeptides.

(e) Characterization of the function and immunogenic potential of individual virus proteins.

(f) Study of the protective immune response with emphasis on the role of cell-mediated immunity.

(g) Support of other initiatives, i.e. development of live attenuated viruses, cell receptors, etc.

2. Dengue

The main aim is to produce second generation vaccines by using the following approaches:

(a) Biochemical definition of principal neutralizing antibody-inducing epitopes on the virus glycoprotein.

(b) Definition of epitopes, which induce the formation of neutralizing versus enhancing antibodies by using monoclonal antibodies.

(c) Viral genome sequencing; cDNA cloning.

(d) Experimental studies of potential vectors, such as bacteria or viruses other than dengue.

(e) cDNA cloning of 17D yellow-fever virus to study its possible use as a vector, by substituting gene sequences coding for epitopes capable of inducing dengue neutralizing antibody.

(f) Generation of non-structural antigens as vaccines.

3. Diseases caused by encapsulated bacteria

The Programme will concentrate on developing vaccines against N. meningitides with a principal focus on oligosaccharide (LOS) antigens. The main goal is to develop an infectious replicating vector, engineered to express antigens which induce protective immunity in children. The strategy includes:

(a) Epidemiological studies of epidemic/endemic disease, with emphasis on immune responses to N. meningitides and other organisms with antigenic determinants shared with virulent Nesseria.

(b) Development of standardized isotype-specific serological tests for bactericidal (protective) antibody.

(c) Biochemical and structural analyses of relevant LOS antigens defined by monoclonal antibody and shown to be involved in protective immunity.

(d) Studies of bacterial genetics to define methods of transferring genes for oligosaccharide expression to potential vector organisms.

4. Hepatitis A and Polio

4.1 Hepatitis A

The Steering Committee recognizes that hepatitis A continues to be a problem in many parts of the world and that the development of a vaccine is highly desirable. The goal of the hepatitis A programme is to develop a cheap, safe and efficacious vaccine suitable for use in the first year of life in all countries of the world and to be included in the WHO Expanded Programme on Immunization. The strategy includes:

(a) The collection of well-characterized strains of hepatitis A viruses of diverse geographical and epidemiological origin.

(b) Studies towards an improved understanding of the pathogenesis and primary sites of replication of the virus.

(c) Establishment of a panel of monoclonal antibodies against hepatitis A virus strains for use in virus characterization and antigen analysis.

(d) Identification of critical antigenic sites of the virus relevant to protective immunity using a combination of selection and non-neutralized mutants in the presence of monoclonal antibodies and recombinant DNA technology.

(e) Molecular cloning and sequencing of the complete genomes of carefully selected hepatitis A strains in order to (i) determine the genetic basis of antigenicity and virulence of the virus and (ii) to rescue infectious virus by transfection to facilitate construction of attenuated strains by strategic modifications of the virus genome.

(f) Development of experimental vaccines using antigens prepared by controlled gene expression and synthesis of oligopeptides.

(g) Study of both humoral and cell-mediated immunity to hepatitis A infections.

4.2 Polio

(a) Determination of the molecular basis of virulence of types 1, 2 and 3 poliovirus with special reference to the Sabin strains and their reversion to virulence.

(b) Application of information from (a) for the development of safety tests of live vaccines employing molecular methods.

(c) Evaluation of prospects for the preparation of new attenuated strains of virus by precise genetic modification (e.g. of Sabin strains).

(d) Evaluation of intratypic recombinant viruses as vaccines or vectors (e.g. for hepatitis A vaccine).

(e) Collection of further data on the molecular basis of antigenicity of poliovirus and the preparation of new immunogens.

5. Tuberculosis

The strategic plan for research on the immunology of tuberculosis was prepared during an informal consultation held in Boston, USA from 7 to 9 February 1983. It was recommended that research should be conducted on the following subjects:

1. Molecular biology
2. Monoclonal antibodies
3. Immunoregulation in human tuberculosis
4. Experimental immunology of tuberculosis
5. Cloning of mycobacteria.

Research proposals, prepared on the appropriate application forms, should reach Immunology, WHO, 1211 Geneva 27, Switzerland, before the deadlines, given below:

Tuberculosis	Dengue	Hepatitis A	Encapsulated bacteria	Acute respiratory viruses
Deadlines (1986)				
2 April	26 March	18 April	9 April	25 April
Dates of Steering Committee meetings (1986)				
2-3 June	26-27 May	16-17 June	9-10 June	26-28 June

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I. Background

1. While UNIDO for reasons of its mandate has an interest in industrial safety practices, it is also aware of the concerns that the World Health Organization (WHO) has in this area as they relate to health and safety. Particular note has been made of the publication Laboratory Biosafety Manual with its guidelines pertaining to laboratory practices, transfer and shipping of specimens, guide to biosafety equipment, etc., and the report by WHO's Regional Office for Europe "Health Impact of Biotechnology". Interests of the two organizations on this important subject led to the establishment in 1982 of continous communications between UNIDO and WHO's programme Safety Measures in Microbiology. During the spring of 1985 it was decided between the two to constitute an informal working group and begin a systematic study on whether a set of biosafety rules and practices could and should be elaborated, the application of which could be recommended to all countries.

2. In May 1985 UNIDO became acquainted with the interest that the United Nations Environment Programme (UNEP) has in the topics of bio-wastes disposal and the deliberate release of genetically engineered organisms into the environment. In view of the obvious overlap of interest, UNEP was informed of the planned UNIDO/WHO working group and asked if it would be interested to partake in its activities. The response was positive and after consultations between UNIDO and WHO, it was decided among the three organizations to constitute an informal UNIDO/WHO/UNEP working group to consider all facets of biotechnology safety pertaining to research institutions, industry and environment, and decided to hold the first meeting at UNIDO headquarters during 27-29 January 1986. The objectives of the meeting were:

(i) To review existing safety practices as they apply to biotechnology R+D and industry.

(ii) To review existing safety rules and regulations that serve to manage biotechnology R+D institutions and bioscience-based industry.

(iii) To review existing practices that attempt to ensure the safety of releasing genetically engineered organisms into the environment.

(iv) As a result of the foregoing, to consider what elements are required for a set of minimal guidelines useful to the managers of the ICGEB and to R+D institutions, especially in the developing countries.

(v) Similar to (iv), to consider what elements are required for a set of minimal guidelines useful to developing countries that may wish to regulate bioscience-based industry and industry that utilizes, or will utilize, biotechnology.

(vi) To determine if guidelines should be formulated that seek to assure safe practices when genetically engineered organisms are, or will be, released into the environment.

(vii) To indicate further activities for each member of the working group and to prepare for the working group's next session.

3. In the early fall of 1985, UNIDO engaged the services of a consultant to prepare a comprehensive study containing: (1) an overview of existing safety practices and regulations that serve to manage biotechnology R+D and industry; (2) an overview of prevalent practices as to the control over releasing genetically engineered organisms into the environment; and (3) recommendations of activities that the informal working group or the ICGEB could undertake with respect to biotechnology safety. This study, "An International Approach to Biotechnology Safety" (see list of documents) was circulated to members of the working group in early January 1986 and was also available at the first meeting.

II. Meeting Activities

4. The meeting took place as planned in conference room VII of the Vienna International Centre. It was opened at 09:30 on 27 January by a member of the UNIDO Secretariat. In attendance were representatives from UNEP, UNIDO, WHO, as well as observers from the FAO and OECD. The list of participants is in Annex I and the list of documents in Annex II.

5. As the first order of business, the draft agenda was presented and adopted (see Annex III for the Agenda). Each agenda item was taken up in turn.

A. Election of a chairman and rapporteur.

Mr. Wafa Kamel of the UNIDO Secretariat was elected Chairman; it was deemed not necessary to elect a rapporteur since UNIDO staff would undertake to write the report of the meeting.

B. Adoption of the draft agenda.

The draft agenda was adopted with no changes.

C. Presentation of the background document: An International Approach to Biotechnology Safety.

6. The UNIDO consultant made an in-depth presentation of his study, An International Approach to Biotechnology Safety. He began by explaining the purpose of the study and his methodology in conducting it. He also explained the general organization of the study, which was to break down genetic engineering into three categories: laboratory research; large-scale operations, which included biowastes; and environmental applications of genetically engineered organisms. For each category, the consultant discussed the current views of the experts on the risks and various regulatory mechanisms for addressing those risks. He also identified common principles in the regulatory mechanisms.

7. The consultant stated that, while individual countries were considering the safety issues raised by genetic engineering, it was also appropriate for international organizations to address these issues from an international perspective because the technology will have worldwide impacts. He also noted certain advantages from international bodies addressing the safety issues of genetic engineering. The major advantage would be the harmonization of regulation. In addition, a costly duplication of effort in risk assessment and guideline development could be avoided. This would be especially valuable for countries with limited resources, which would be better off directing those resources toward local genetic engineering efforts.

8. The following activities were proposed for the ICGEB or the Informal Working Group:

(1) Act as a forum for information exchange and debate;

(2) Study potential risks and make findings regarding actual hazards or areas where additional research is needed;

(3) Develop risk assessment methodology;

(4) Conduct risk assessment;

(5) Develop safety guidelines for the various categories of applications of genetically engineered organisms;

(6) Assist other countries, especially less developed countries, in adapting the guidelines to their own special needs; and

(7) Train scientists, technicians, workers, and other support staff to handle genetically engineered organisms safely.

9. The consultant discussed which of the recommended actions were, in his opinion, most appropriate for either the ICGEB or the Informal Working Group. He stated that 1 would be most appropriate for the Informal Working Group and 6 and 7 would be most appropriate for the ICGEB. He stated that both organizations could be involved with 2-5, although 2-4 would probably be more appropriate for the ICGEB, and 5 would be very appropriate for the Informal Working Group, since it could begin this activity immediately.

10. After the report had been discussed by the participants, the UNIDO representatives presented UNIDO's views on biosafety. It was noted that UNIDO has since its inception been involved in several aspects of applied microbiology. However, after 1981 this type of activity has been significantly expanded as the organization initiated a series of measures, the objective of which were, and remain, to make certain that the fruits likely to emanate from advanced biotechnology R+D, including genetic engineering, will be shared by developing countries. The most important initiative being undertaken is to establish and make operational the International Centre for Genetic Engineering and Biotechnology (ICGEB) in two components located in New Delhi, India and Trieste, Italy. As of this writing, 36 countries belong to the ICGEB and several more will undoubtedly join in the near future. Further, operational activities will begin in provisional ICGEB facilities as early as the beginning of 1986.

11. During the preparatory work for the ICGEB, the matter of safe laboratory practices, especially as they pertain to research on genetically engineered microorganisms, became a matter of concern to UNIDO. As several countries offered to host the ICGEB and/or its affiliated centres, it became clear that national rules or guidelines that were aimed at ensuring safe laboratory practices varied from almost no control to control measures akin to the U.S. or U.K. guidelines. As the time grows ever shorter before research begins at both ICGEB components and at its affiliates, the matter of drawing up and applying an adequate and uniform safety rules and practices throughout the ICGEB system takes on an air of urgency. Further, since research at the ICGEB and its affiliates is to be of an applied nature, and since products and processes will ensue as soon as practicable, there is also a need to consider safety rules and practices as they may be applicable to bioscience-based industry (and to industry which will utilize the advanced biotechnology techniques).

D. Presentation of position or concept papers by representatives from WHO and UNEP.

12. The representative from WHO Headquarters presented his Organization's view on biosafety, particularly as they touch on the manufacture of vaccines and biologicals. He noted that recent advances in molecular biology have prompted the WHO to assess them in reference to public health applications. Primary considerations have been infectious diseases. As a result, new or expanded initiatives have been established within WHO's Division of Communicable Diseases. These include:

(a) WHO Programme for Vaccine Development (see list of documents);
(b) New rapid diagnostic techniques;
(c) Transfer of vaccine production technology to developing countries.

13. With these initiatives there is the commitment of the Organization to assure the safety of the product, the safety of the biotechnology industry worker, and the safety of the community from possible hazardous discharges from the industry.

14. WHO is called on by its constitution "...to develop, establish and promote international standards with respect to...biological...products." Accordingly, WHO sets international biological standards and provides relevant information to national health authorities so that national standards, calibrated in international units, can be established. Through this process WHO seeks to assure that vaccines and other biological products developed through its programmes, and others, offered through international trade will be safe for use by the general public.

15. To meet the worker and community safety requirements, WHO's Seventh General Programme of Work calls for the provision of safety guidelines for biotechnology organizations producing vaccines and biological products. Accordingly draft biosafety guidelines are being considered for laboratories and industries engaged in the manufacture or preparation of vaccines and biologicals, where:

1. The process uses organisms or cells that contain foreign DNA inserted by the recombinant DNA technique;

2. The volume of culture, medium or tissue is larger than 10 litres. This definition includes the use of continuous culture where the volume of the culture vessel or of the spent culture is greater than 10 litres; and

3. The work is carried out within contained facilities.

16. While the proposed guidelines are primarily directed towards fermentation technology, the containment specifications and other practices may be used as a basis to derive similar containment standards for other technologies. The guidelines apply only to minimum practices and physical containment.

17. Existing national guidelines for large scale production of vaccines and biological products are serving as the basis of the WHO effort. However, development of the WHO guidelines is currently in abeyance to ascertain if similar guidelines being developed by the OECD or under discussion with UNIDO and UNEP would serve WHO's needs.

18. Next, the WHO representative from the Regional Office for Europe spoke. He explained that the Environmental Health Service of WHO, Regional Office for Europe, includes in its work the impacts of air, food, water, housing waste, and occupational environments on health. Its work covers both chemical and physical safety. Biosafety has been given special consideration, especially as it pertains to food, water waste and housing. Due to the great interests of the member states of the Region on safety aspects and possible adverse impact on human health of new developments in biotechnology, a working group on Health Impact of Biotechnology was organized in Dublin, Ireland during 1982. The recommendations of the group (WHO/EURO Interim Document 16) refers to both occupational and environmental concerns of new developments of biotechnology. Because of the presence of several uncertainties and in view of the rapid development of the field, it was considered necessary to have a follow-up review on the same subject; a review meeting is now scheduled to be held during the second half of 1986.

19. The Regional Office of WHO/EURO is especially concentrating its attention on the possible adverse human health impact of the manipulation of genetic material in the laboratory, the industrial and environmental applications of biotechnology, including those posed by biological waste.

20. The Environmental Health Service of WHO/EURO has also a strong interest in any research programmes covering health impact assessments of the developments in biotechnology.

21. The Environmental Health Service does not include in its programmes any technological development or assessment of biotechnology systems or products. The latter of these is part of the Regional Programme on Appropriate Technology for Health under its activities on biosafety, which has in the past also been working wih some aspects of safety of biotechnology.

22. Due to their global nature, the ethical issues, being inherent parts of the new developments in biotechnology, are considered as belonging to the mandate of the WHO Headquarters.

23. The view of UNEP was expressed by its representative. He made the following points:

(a) Although biotechnology with its advanced techniques of genetic engineering could generate considerable rewards for humanity, the transfer of genetically manipulated organisms (microorganisms, plants, animals, cell lines and hybridomas) from the carefully controlled laboratory bench and factory where they have been produced to the environment for agricultural, industrial or other benefits is gathering scientific, public and political concerns as man, animal, plant and other ecosystem populations will be exposed to uncommonly large numbers of such organisms. In fact, the critical area in terms of safety issues concerns will be the environment.

(b) The fact that no single health incident has been reported since the commencement of recombinant DNA in the last decade could be attributed to mainly the guidelines developed at that time. They led to strict control on the types of experiments to be conducted and specified containment procedures. In fact, as none of the postulated dangers has materialized, guidelines developed by many agencies are now being relaxed.

(c) Relative to safety considerations associated with laboratory scale and large scale industrial applications little attention was paid to environmental and agricultural applications of genetically manipulated organisms. There is a need for adequate safety measures, guidelines and regulatory actions for the production, field testing and release of genetically manipulated microorganisms in the environment. In fact, as such organisms will be engineered mainly to spread and perform their desired function in the environment (uncontained applications) they will intereact with the ecosystem and potential risks that may be associated with their release will have thus to be evaluated.

(d) A methodology for assessing any potential risk in releasing genetically manipulated organisms (including those produced by conventional methods) in the environment (as compared to laboratory and industrial scales) needs to be developed, so that properly designed uniform guidelines consistent with the level of anticipated risk could be developed.

(e) At present scientific basis for risk assessment involves: (i) hazard identification; (ii) dose - response assessment; (iii) exposure assessment; followed by (iv) risk characterization. Once the risk is characterized alternative regulatory actions could then be evaluated for selecting among them (risk management). In case of environmental applications of genetically manipulated organisms, quantitative risk assessment following the above mentioned approach will be rather difficult for many reasons, including among others:

(i) Lack of reliable sufficient data;

(ii) Lack of data on long term effects;

(iii) Relatively small size of researchers and workers engaged in this field and so assessment would be insignificant;

(iv) Risks likely to be associated with the release of a given organism will differ from one case to the other;

(v) Difficulty in predicting the fate and effects of released organisms;

(vi) Secrecy associated with recombinant DNA technology;

(vii) Absence of monitoring procedures.

(f) Ecological analysis of the likely consequences of releasing genetically manipulated organism in the environment is lacking and is needed on a case by case basis.

(g) The first initial step towards the qualitative (rather than quantitative) assessment of potential risks associated with release of genetically manipulated organisms in the environment would be to conduct a detailed study on successful and unsuccessful introduction of alien organisms in the environment (e.g. bioinsecticides, biofertilizers, new plant varieties, etc.), with the aim of developing conjectural prediction methods. The results of such a survey would provide a data base for follow-up activities, particularly with regard to the development of risk assessment methodology and, hence, safety guidelines.

E. Presentation of Concept Papers by Observers.

24. The observer from OECD made an informal presentation of the OECD study of biotechnology safety issues. The study considers the risks and benefits of industrial and environmental applications of recombinant DNA technology. It sets forth scientific considerations for evaluating the risk of organisms containing recombinant DNA. These are not regulatory standards, but rather guiding principles. She also noted that for industrial applications most organisms would require only minimum containment and that with respect to environmental applications the OECD working group had decided that it was too early to be able to develop guidelines. The OECD working group recommended, among other things, that the OECD continue to watch recombinant DNA technology and that industry use low risk organisms as much as possible. The study was approved by the OECD Committee for Scientific and Technological Policy on 5 February 1986). The observer from FAO stated his organization's interests on the subject. The FAO would like to follow further developments and would probably like to take part in the formulation of safety rules or guidelines.

F. Discussion of Risks and Regulations Pertaining to Laboratory Work.

25. The participants discussed risks and regulations pertaining to laboratory scale applications of genetic engineering. One question was whether actual safety practices could be measured in laboratories. This involved a discussion of the WHO guidelines for good microbiological practices and the extent to which they were being used, particularly in developing countries. The WHO representative stated that he would attempt to do a preliminary survey among his colleagues in the field to assess the extent of use of these guidelines.

G. Discussion of risks and regulations pertaining to large scale biotechnology processes.

26. It was agreed among all present that industrial practices wherein the use of "traditional" techniques and microorganisms has proven to be safe. It was the sense of the meeting that good manufacturing practices properly followed and properly applied to large-scale processes involving genetically engineered organisms, would adequately address any risks presented

by those processes. However, it was noted that there was not yet sufficient experience and data from which definitive conclusions could be drawn about the long-term effects of such processes. Questions also arose about whether wastes from large-scale industrial practices using genetically engineered organisms pose hazards to humans or the environment.

27. The matter whether existing national rules and legislation are adequate to safely manage bioscience-based industry had to be left open. Though it was felt that existing rules and regulations pertaining to good manufacturing practices are probably adequate if properly followed, in the industrialized countries, the situation is much less clear in the developing countries.

28. It was agreed that UNIDO would endeavour to undertake a project in reference to biowastes disposal, while WHO would survey laws directly or indirectly pertaining to biotechnology and its applications (see item J below).

H. Discussion of conjectural risks of environmental applications and the regulations thereof.

29. Whether or not hazards are posed to man and the environment by the deliberate release of genetically engineered organisms is a wide open question. The UNEP representative observed that much information is available about the effects of deliberatively released bioactive substances or agents into the environment, such as biofertilizers, biopesticides, new species of plants, etc. However, this information may not have been appropriately collected and analyzed in a manner to be a useful base for assessing the safety of releasing genetically engineered organisms into the environment.

30. As pointed out by the UNIDO consultant, examples exist where organisms that have been accidentally or otherwise released into a new environment have had deleterious impacts. He pointed out that it would be useful to design a model project to try to determine how organisms establish themselves in a new environment. If such information was available and an information base existed on the lines suggested by UNEP, it could be possible to develop guidelines to guide those who will find it useful to release genetically engineered organisms into the environment. In view of the need for more information, the UNEP representative proposed the undertaking of a project that would have as its objective the study of releasing genetically engineered into the environment (see item J below).

I. Elements to Construct Minimal Guidelines.

31. The Participants considered the issue of what elements were necessary for minimal guidelines for laboratory and industrial scale facilities. It was suggested that guidelines from various countries relating to genetic engineering or microbiology be collected and reviewed to determine their similarities and differences. UNIDO could collect the guidelines by sending written requests to the appropriate governmental body in the countries. The results of the analysis of the guidelines could be used to prepare a first draft of model guidelines, which could then be presented to a group of experts for further work and finalization.

J. Recommendations.

32. The following recommendations were accepted by the Informal Working Group:

(i) A project will be undertaken to develop minimal guidelines for laboratory and industrial scale facilities. In so doing, various national guidelines and guidelines and/or principles proposed by international organizations will be collected and abstracted, with explanations as to why guidelines differ, in order to prepare a first draft of model guidelines. The draft will be discussed and finalized at a workshop of experts in different disciplines and perspectives on the issue of safety, especially in developing countries. UNIDO will be the lead agency in carrying out this project, but with equal input from UNEP and WHO.

(ii) A project will be undertaken to assess whether biowastes from large-scale industrial practices where genetically engineered organisms are used may pose hazards to man or the environment.

This project will require the services of two consultants and will take approximately four man-months, including travel. UNIDO will be the lead agency for this project in close cooperation with UNEP.

(iii) UNEP would act as a leading agency (in co-operation with UNIDO) for the preparation of a study on the successful and unsuccessful release of genetically manipulated organisms (microorganisms, plants, animals, insects, etc. manipulated by conventional or advanced techniques) into the environment (e.g. application of bioinsecticides, biofertilizers, etc.).

This might be achieved through the organization of an expert group meeting where experts will be invited to prepare discussion papers on selected topics followed by the production of a detailed report including recommendations for future actions. Special emphasis will be placed on cases relevant to developing countries.

(iv) UNEP will sponsor a round table discussion on the subject in association with the International Conference on Microbial Ecology to be held in August 1986 in Yugoslavia. Working Group members are invited to participate.

(v) If circumstances allow, UNEP would undertake, in collaboration with its Law Unit, a survey of environmental protection acts already existing in developing and developed countries and the status of their implementation.

(vi) The Working Group agrees that it would be helpful to assess or determine the awareness of biosafety or laboratory safety, particularly in developing countries. The WHO in the past few years has published the WHO Laboratory Biosafety Manual and conducts several biosafety "Train the Trainer" courses. The WHO therefore will survey the impact of these efforts by several means which will include:

(a) Number of manuals distributed;
(b) Programme reviews by its six regional offices;
(c) Assessments by its biosafety collaborating centres, biosafety instructors and participants in the training programmes.

(vii) It was agreed that a review of existing biotechnology legal requirements on a global basis is required. WHO agreed to attempt such a review through information compiled by its Health Legislation Unit. Information regarding national laws, rules or regulations pertaining to biotechnology, including aspects of the technology relating to worker health and safety and environmental protection will be gathered and compiled on a country by country basis.

(viii) WHO has established four biosafety collaborating centres at institutions with expertise in biosafety training, research, and consultation. Their services are made available to member states. These centers are located at the Center for Disease Control CDC, Atlanta, USA; National Institute of Health (NIH), Bethesda, USA; Laboratory Center for Disease Control (LCDC) Ottawa, Canada; and Fairfield Hospital, Melbourne, Australia. The LCDC and NIH have specific expertise in industrial applications of biotechnology. Other institutions with expertise are the National Institute of Virology, Pune, India; NIH, Tokyo, Japan; and the National Bacteriology Laboratory, Stockholm, Sweden. It is suggested that it would be possible to "twin" these institutions with designated affiliated centers of the ICGEB for development of expertise in biotechnology safety programmes for developing countries. A project to do so will be designed.

33. All the foregoing recommendations are to be implemented by the time of the second meeting of the Informal Working Group.

K. Other matters.

(i) The Informal Working Group decided to invite the FAO and the ILO (International Labour Organization) to join it.

(ii) It was decided to hold the second meeting of the Informal Working Group during 3-5 November 1986. The venue will be Geneva, Switzerland.

Annex I

List of Participants

1. Members of the Informal UNIDO/WHO/UNEP Working Group

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Annex II

List of Documents

	Aide-Memoire
UNIDO/IS.627	An International Approach to Biotechnology Safety
ID/WG.463/1	Safety Guidelines and Procedures for Bioscience-based Industry and other Applied Microbiology
ID/WG.463/2	Biosafety Guidelines for Manufacture of Vaccines and Biologicals
Background Papers:	Health Impact of Biotechnology, WHO Regional Office for Europe, 1984.
	Safety Considerations for Industrial, Agricultural and Environmental Applications of Organisms Derived by Recombinant DNA Techniques, prepared by the Committee for Scientific and Technological Policy, OECD

Annex III

Agenda

A. Election of a chairman and rapporteur.

B. Adoption of the draft agenda.

C. Presentation of the study "An International Approach to Biotechnology Safety" by UNIDO consultant. Discussion of the study.

D. Presentation of position or concept papers by representatives from WHO and UNEP.

E. Presentation of position or concept papers by other representatives and observers.

F. Discussion of risks and regulations pertaining to laboratory R+D.

G. Discussion of risks and regulations pertaining to large scale biotechnology processes.

H. Discussion of conjectural risks of environmental applications and the regulation thereof.

I. Consider elements required to construct minimal guidelines for biotechnology R+D facilities and for industry using biotechnology.

J. Formulate recommendations for activities to be undertaken by the members of the informal working group before its next session.

K. Other matters.

L. Close of the meeting.